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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,326	02/22/2005	Mayumi Saki	506.44792X00	8611

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EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	**PAPER NUMBER**
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,326	SAKI ET AL.	
	Examiner	Art Unit	
	Charleswort Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1-8 and 10-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9, 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response without traverse to the Restriction/Election requirements, filed 2/12/07, electing Group IV, and nitrogen-containing tricyclic compound represented by formula 1, is acknowledged and made of record.

Status of Claims

Claims 1-25 are pending in this application and are the subject of this Office action.

Claims 1-8, and 10-21 are withdrawn for purposes of examination for being directed to non-elected subject matter.

Claims 9, and 22-25 are presented for examination.

Minor Objections

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computed tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is need for consulting the full patent text for details. In the instant case, abstract exceeds the 150 words limits. Applicant's cooperation is requested in correcting this deficiency in the abstract.

Nonstatutory Obviousness-Type Double-Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 9, and 23-25, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-10, 13-16, and 27-28 of copending U.S. Patent Application No, 10/525,324 ('324), in view of Kay (Kay, A.B. Allergic diseases and their treatment. N. Engl. J. Med. 2001;344(2):109-113). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims.

In particular, reference claims 4-8 of '354 are directed towards the identical nitrogen-containing tricyclic compound of formula I of the instant application; reference claims 9-10, 14-16, and 27-28 are directed to pharmaceutical compositions comprising a compound of formula I; reference claim 13 is directed towards a method for prevention and/or treatment of itching comprising administering an effective amount of a compound of formula I.

Kay teaches that intrinsic asthma may be associated with local production of IgE antibodies against unknown antigens and that immunologic triggers have a role in both nonatopic and atopic asthma (page 110, column 1, lines 13-16). Kay teaches that urticaria (widespread, itchy wheals or hives) and angioedema (deep mucocutaneous swelling) often occur together (page 111, column 1, last paragraph, lines 1-3). Kay teaches that urticaria is often IgE-mediated (page 111, column 1, last full paragraph, lines 4-5). To the extent that IgE is involved in urticaria and allergic asthma, both groups overlap.

Thus, someone of skill in the art at the time the instant invention was made would have deemed it obvious to create the instant invention with a reasonable expectation of success in view of Kay.

This is a provisional obviousness-type double patenting rejection because the conflicting claims of the copending application have not in fact been patented.

Claim rejections – 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 9, and 23-25 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses specific compounds with complete chemical structures of general formula I, which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 9, and 23-25 are directed to encompass drugs which only correspond in some undefined way to the specifically instantly disclosed chemicals with respect to optional groups e.g. R1, R2, R3, R4, X, n, and Y. None of these drugs meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and

chemical structures are highly variant and encompass a myriad of possibilities. To the extent that no structure-function data is disclosed to reasonably correlate the critical chemical feature of these compounds with the contemplated treatment effect to be achieved, the specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed drugs with incomplete chemical strucutures, derivatives, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the specifically defined disclosed chemical species of formula I, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 9 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of synthesizing compounds of formula I and a method of treating mice using compound 1, does not reasonably provide enablement for preventing or treating asthma with certain compounds in any subject. This is a scope enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

Applicant discloses study results obtained after intraperitoneally injecting BALB/c male mice with 30 mg/kg of compound 1 with respect to effects of compound 1 on antigen-induced bronchoconstriction, airway hyperactivity and eosinophil infiltration in airway; prednisolone 100 mg/kg was administered orally to mice as the reference drug (Patent Application Publication US 2006/0239999 A1; page 32, paragraph 0305 to page 33, paragraph 0313). Applicant asserts that "[f]rom the ...results, it has been suggested that a substance capable of suppressing the function involved in signal transduction of protein comprising an amino acid sequence represented by SEQ ID No: 11 is useful as an agent for treatment of itching (page 33, paragraph 0314).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the pharmaceutical art is generally unpredictable, requiring each embodiment to be individually assessed for physiological activity. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)). For example, despite the development and publication of clinical guidelines regarding t treatment of asthma, several challenges still plaque clinicians when it comes to appropriate therapy for asthma and COPD (Schoening. Issues and challenges for managed care in the treatment of asthma and chronic obstructive pulmonary disease. The American Journal of Managed Care. 2004; 10:S158-S163; see page S159, column 2, second full paragraph.)

Tarasova et al. (US Patent 7,105,488 B1) teach methods for inhibiting the biological activity of a target G-protein-coupled receptor (GPCR) by contacting a cell that expresses GPCR with an isolated GPCR-modulating molecule comprising a peptide (see claims 1-4).

Harrison's Principles of internal Medicine teaches that from an etiologic standpoint, asthma is a heteregenous disease: namely, allergic and idiosyncratic asthma (Harrison's Principles of Internal Medicine.1992: pages1167-1172; see page 1167, column 1, paragraph 1 to column 2, first full paragraph). Harrison's teaches that a number of causes have been postulated for the increased airway reactivity of asthma; however, the basic mechanism remains unknown (page 1167, column 2, 4th full paragraph, lines 1-2).

2. The breadth of the claims

The claims are relatively broad. For example, claim 9 recites the term "prevention," which is reasonably construed to encompass subjects without the disease. However, applicant has not disclosed any data to support this assertion. The discussion above regarding the written description rejection is incorporated by reference. Because the therapeutic response to be achieved would necessarily vary depending upon the particular cause of the asthma, the level of predictably in practicing the claimed invention would be greatly diminished.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the

particular administration regimens (dosages, timing, administration routes etc.) necessary to treat and/or prevent asthma. The 'working examples" are limited to example administration of compound 1 to mice and evaluation of the effects of compound 1 on antigen-induced bronchoconstriction, airway hyperactivity and eosinophil infiltration in airway; prednisolone 100 mg/kg was administered orally to mice as the reference drug (Patent Application Publication US 2006/0239999 A1; page 32, paragraph 0305 to page 33, paragraph 0313). No reasonably specific guidance is provided concerning useful therapeutic protocols or specific agents for treating asthma.

4. The quantity of experimentation necessary

In view of the fact that appropriate dosage duration and agent selection still remain major hurdles in treating asthma, it is reasonable to surmise that this level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention in patients (Schoening, page S159, column 1, second full paragraph, lines 6-13).

Thus, based on the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed methods could be predictably used as treatments for treating and/or preventing asthma.

For the reasons stated above, claims 1-2 and 8-17 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9, and 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9, 23-25 recite the term "and/or." This term is indefinite because this term is ambiguous. It is suggested that this specific rejection may be overcome by amending the claims to either deleting the term "and" or the term "or."

Claim 9 and 25 recites the term "Z1 and Z2 are combined together with two carbon atoms being adjacent to each of them to form a substituted or unsubstituted ring or substituted or unsubstituted hetercycle." This term is vague and indefinite because it is not clear, for example, how the combining of Z1 and Z2 with two carbon atoms will result in a substituted hetercyle.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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26 April 2007
CER

BRIAN-YONG S. KWON
PRIMARY EXAMINER